REMARKS

Claims 2-5, 7, 9, 10, 12, 20, 25, 26, 32-50, 54, 57, 57, and 59 have been canceled or withdrawn from consideration. Claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55 and 58 remain pending. Claims 17, 19, 24, 52, 55, and 58 are currently amended. Support for the amendments can be found in the specification as filed, for example, on page 1 lines 11-16, page 31, page 38 lines 29-31, figures 9A, 10A, 11 and 12, and Tables I and II. Therefore, no new matter has been introduced herewith. The following addresses the substance of the Office Action.

Rejection under 35 U.S.C. §112

The Examiner rejected Claims 30 and 31 under 35 U.S.C. §112, first paragraph, for allegedly lacking written description. More specifically, the Examiner indicated that Claim 30 was rejected because the specification does not describe the structure of the endogenous inducer of dendritic cell migration and maturation, and Claim 31 was rejected because the specification does not describe the expression of the adhesion molecule. The Examiner cited University of California v. Eli Lilly and Co. (119 F.3d 1559, 43 USPQ2d, 1398-1412, Fed. Cir. 1997) and Enzo Biochem Inc. v. Gen-Probe Inc. (63 USPQ2d, 1609-1618) in support for this rejection. Applicant respectfully disagrees.

The cited case law states that "a written description of an invention involving a chemical genus, like a description of chemical species, requires precise definition, such as structure, formula or chemical name of the claimed subject matter to distinguish it from other materials" (emphasis ours). The subject matter of Claims 30 and 31 is the method of vaccinating a mammal. Claims 30 and 31 are not claiming the endogenous inducer of dendritic cell migration and maturation, or the adhesion molecule. Therefore, Applicant respectfully suggests that the cited case law is not applicable to the instant case. Furthermore, the specification provides a sufficient list of endogenous inducers of dendritic cell migration and maturation (24:18-28) and adhesion molecules (1:26-27; 2:1-7; 28:21-22) to show possession (written description) of the claimed invention and to enable anyone with an ordinary skill in the art to practice the claimed method. Accordingly, Claims 30 and 31 are fully supported by the specification as filed, and Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §102

The Examiner rejected Claims 1, 6, 8, 11, 13, 14, 16, 28, 29, 30, 31, 55 and 56 under 35 U.S.C. §102(b) as being allegedly anticipated by Dearman et al. (Fundamental and Applied Toxicology, 1996, Vol. 33, pp. 24-30). Applicant respectfully disagrees.

To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Claim 1 recites "[a] method for vaccinating a mammal against an antigen, comprising: introducing into the mammal an effective dose of the antigen or an epitope(s) thereof; and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introducing the antigen and administering the treatment are performed independently in any order, wherein the antigen or epitope(s) thereof is ***introduced into the mammal by disrupting the stratum corneum***, wherein the topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and inducing dendritic cells to migrate to the draining lymphoid organ, and wherein said lipophilic molecule is ≤500 daltons and is selected from the following formulas..." (***emphasis added***).

Among other deficits, Dearman fails to teach vaccination against a target antigen, ***wherein the antigen is introduced into the mammal by disrupting the stratum corneum***. Accordingly, because Dearman does not teach each and every element of Claim 1, Dearman cannot anticipate Claim 1, or Claims 6, 8, 11, 13, 14, 16, 28, 29, 30 and 31, which depend therefrom.

Amended Claim 55 recites "[a] method for vaccinating a mammal against a target antigen, comprising: ***injecting the mammal*** with an effective dose of said target antigen or an epitope(s) thereof; and administering internally to the mammal a treatment in an amount sufficient to increase the number of dendritic cells presenting said target antigen in a lymphoid organ, wherein the treatment comprises a lipophilic molecule with a molecular weight of ≤500 daltons, which in the absence of an antigen is capable of inducing immature dendritic cells to

mature and migrate to the draining lymphoid organ, and wherein said lipophilic molecule is selected from the following formulas..." (***emphasis added***).

Among other deficits, Dearman fails to teach vaccination against a target antigen, comprising ***injecting the mammal*** with an effective dose of said target antigen. Accordingly, because Dearman does not teach each and every element of Claim 55, Dearman cannot anticipate Claim 55. Claim 56 has been canceled.

Thus, Applicant respectfully requests withdrawal of the rejections of Claims 1, 6, 8, 11, 13, 14, 16, 28, 29, 30, 31 and 55 under §102.

Rejections under 35 U.S.C. §103

The Examiner rejected Claims 1, 6, 8, 11, 13, 14, 16, 17, 21, 22, 27-31, 51, 55 and 56 under 35 U.S.C. §103(a) as being allegedly obvious over Dearman et al. in view of Mitragotri et al. (WO 97/04832) and Paul et al. (Vaccine research, 1995, Vol. 4, pp. 145-164).

Under MPEP §2143, "[t]o establish a *prima facie* case of obviousness... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure..."

Claim 1 recites "[a] method for vaccinating a mammal against an antigen, comprising: introducing into the mammal an effective dose of the antigen or an epitope(s) thereof; and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introducing the antigen and administering the treatment are performed independently in any order, wherein the antigen or epitope(s) thereof is ***introduced into the mammal by disrupting the stratum corneum***, wherein the topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and inducing dendritic cells to migrate to the draining lymphoid organ, and wherein said lipophilic molecule is ≤500 daltons and is selected from the following formulas..." (***emphasis added***).

As discussed above, Dearman fails to teach inter alia, vaccination against a target antigen, wherein the antigen is ***introduced into the mammal by disrupting the stratum corneum***. Paul teaches vaccinating using topical delivery of an antigen across the intact skin using submicroscopic transfersome vesicles. Mitragotri teaches transdermal transport of proteins across intact skin using ultrasound. Neither Paul nor Mitragotri teach or suggest introducing the antigen into the mammal by disrupting the stratum corneum. Indeed, both these secondary references, as well as Dearman, teach methods of introducing antigens, which expressly avoid disrupting the stratum corneum. Thus, because the combination of references fails to teach or suggest all of the claim limitations, Applicant respectfully asserts that the Examiner has failed to make out a *prima facie* case of obviousness.

Furthermore, there is no teaching or suggestion in the references themselves to motivate the skilled artisan to modify the prior art methods to include a step of introducing the antigen by disrupting the stratum corneum. In fact, all three of these references teach away from such a modification. For example, while Dearman teaches that topical dibutylphthalate (DBP) fails to induce migration of Langerhans cells from the skin to draining lymph nodes, Dearman suggests that DBP may enhance the immune response to contact hypersensitivity antigens, like FITC, by increasing permeation of the chemical allergen through intact skin. Likewise, both Paul and Mitragotri teach methods designed to avoid disrupting the stratum corneum. To include a step of disrupting the stratum corneum in these prior art methods would be inconsistent and/or redundant with the respective uses of DBP (Dearman), transfersomes (Paul) and ultrasound (Mitragotri)—each of which are taught as facilitating permeation of antigen through intact (i.e. non-disrupted) skin. Thus, the cited references would teach the skilled artisan to avoid Applicant's recited step of introducing an antigen by disrupting the stratum corneum. Accordingly, Applicant respectfully requests withdrawal of the §103 rejections of Claims 1, 6, 8, 11, 13, 14, 16, 21, 22, and 27-31 over Dearman in view of Paul and Mitragotri.

Amended Claim 17 recites "[a] method for vaccinating a mammal against a target antigen, comprising: introducing into the mammal an effective dose of said target antigen or an epitope(s) thereof; and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells presenting said target antigen in a lymphoid organ, ***wherein the topical treatment in the absence of an antigen is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ***,

wherein introducing said target antigen and administering the treatment are performed independently in any order, and ***wherein the topical treatment comprises application of ultrasound energy***.

The primary reference fails to teach the use of ultrasound as a topical treatment which in the absence of antigen induces the maturation and migration of immature dendritic cells. Although Mitragotri teaches the use of ultrasound to enhance permeation of proteins through intact skin, Applicant respectfully asserts that one skilled in the art would find neither a motivation to combine the references, nor any expectation of success in coming up with Applicant's claimed invention for the following reasons. Dearman discloses that topical DBP in acetone has no influence (Figure 3a, Table 2 lines 1 and 2) on the migration of Langerhans cells from the skin to draining lymph nodes. Dearman further teaches that DBP is "a chemical that lacks contact allergic potential" (see Dearman p. 24), and is not an antigen because... "[i]n the absence of [an antigen] FITC, application to mice of DBP dissolved in acetone was unable, at any concentration examined, to induce [lymph node cells] LNC proliferative responses" (see Dearman p. 25 and Fig. 1). In the presence of an antigen (FITC), however, Dearman teaches that DBP enhances the permeation and acquisition of antigen (FITC) by Langerhans cells. Accordingly, one skilled in the art would conclude from a careful review of Dearman that a topical permeation enhancer, like DBP, which lacks contact allergic potential, would fail in the absence of an antigen to induce the maturation and migration of dendritic cells to draining lymphoid organs.

The skilled artisan familiar with the teaching of Dearman, would likely conclude that Mitragotri merely teaches an alternate means of enhancing antigen permeation through intact skin—namely ultrasound energy. Mitragotri is silent as to whether ultrasound has any influence on the maturation and migration of dendritic cells to draining lymphoid organs in the presence or absence of antigen. One skilled in the art would infer that ultrasound, like DBP in Dearman, would fail in the absence of an antigen to induce the maturation and migration of dendritic cells to draining lymphoid organs. Thus, the references themselves contain no motivation for the skilled artisan trying to develop a vaccination method to substitute one permeation enhancer for another, since it is the contact hypersensitivity antigen according to Dearman and not the permeation enhancer that causes migration of Langerhans cells to draining lymph nodes.

Even assuming *arguendo* that a skilled artisan were to arbitrarily substitute ultrasound for Dearman's DBP, one would have NO expectation of success in obtaining a topical treatment which in the absence of antigen is capable of inducing maturation and migration of immature dendritic cells, because Mitragotri is silent and Dearman explicitly teaches that DBP fails (at any concentration) to induce maturation and migration of Langerhans cells in the absence of antigen (FITC).

Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claim 17 over Dearman in view of Paul and Mitragotri.

Both independent Claims 51 and 55 recite methods for vaccinating a mammal against a target antigen, comprising: "***injecting the mammal*** with an effective dose of said target antigen or an epitope(s) thereof...". As detailed above with regard to Claim 1, none of the cited references teach methods of introducing the target antigen via injection. Instead, Dearman, Paul and Mitragotri uniformly teach methods of introducing the target antigens via permeation through intact skin. Thus, as discussed above, these references teach away from the claimed methods. It is also noted that amended Claim 55 has the further limitation of "...***administering internally to the mammal a treatment...***". None of the references teach internal administration of an inducer of Langerhans cell migration. Accordingly, because not all of the elements of the claimed inventions are disclosed in the combination of references, the Examiner has failed to state a *prima facie* case of obviousness. Claim 56 has been canceled.

In view of the foregoing, Applicant respectfully requests withdrawal of the §103 rejections of Claims 51 and 55 over Dearman in view of Paul and Mitragotri.

The Examiner rejected Claims 1, 18 and 24 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of King et al. (Vaccine, 1987, Vol. 5, pp. 234-238).

As detailed above, Claim 1 and dependent Claim 18 are patentable over Dearman in that Dearman fails to teach or suggest a step of introducing the target antigen by disrupting the stratum corneum. King does not cure this defect, as King teaches another antigen delivery method which avoids disrupting the stratum corneum (i.e., introducing the antigen via the nasal mucosa). Thus, the combination of Dearman and King fail to teach or suggest every element of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claims 1 and 18 over Dearman in view of King.

Claim 24 has been amended to recite "[a] method for vaccinating a mammal against an antigen, comprising: introducing into the mammal an effective dose of the antigen or an epitope(s) thereof; and administering to the mammal a topical treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells in a lymphoid organ, wherein introducing the antigen and administering the treatment are performed independently in any order, wherein said topical treatment comprises a lipophilic molecule capable of traversing the stratum corneum and inducing dendritic cells to migrate to the draining lymphoid organ, and wherein the antigen or epitope(s) thereof is ***introduced into the mammal by disrupting the stratum corneum*** and transferring cells comprising the antigen or epitope(s) thereof."

Applicant respectfully asserts that Claim 24 as amended is patentable over Dearman in that Dearman fails to teach or suggest a step of introducing the target antigen by disrupting the stratum corneum and transferring cells comprising the antigen. King teaches another antigen delivery method which avoids disrupting the stratum corneum (i.e., introducing the antigen via the nasal mucosa). Because King fails to provide the missing teaching related to disruption of the stratum corneum, the combination of Dearman and King fail to teach or suggest every element of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claim 24 over Dearman in view of King.

The Examiner rejected Claims 1, 18, 19, 23 and 27 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of Salyers et al. (Bacterial Pathogenesis, 1994, pp. 8-14 and 144-145).

Claims 1, 18, 23, and 27 recite a vaccination method comprising a step of introducing an antigen or epitope thereof into a mammal by disrupting the stratum corneum. As detailed above, Dearman teaches that Langerhans cell acquisition of a contact hypersensitivity antigen can be facilitated by DBP by increasing permeation of such antigens through intact skin. Salyers teaches that an antigen can be introduced into a mammal by ingestion. Because neither Dearman nor Salyers teach or suggest a vaccination method in which antigen is introduced into a mammal by disrupting the stratum corneum, the combination fails to set forth a *prima facie* case of obviousness. Indeed, as discussed above, the cited prior teaches away from methods that include a step of disrupting the stratum corneum. Accordingly, Applicant respectfully requests

reconsideration and withdrawal of the §103 rejection of Claims 1, 18, 23 and 27 over Dearman in view of Saylers.

Amended Claim 19 recites: "[a] method for vaccinating a mammal against a target antigen, comprising: introducing into the mammal an effective dose of said target antigen or an epitope(s) thereof; and administering internally to the mammal a treatment in an amount sufficient to increase the number of antigen-bearing dendritic cells presenting said target antigen in a lymphoid organ, wherein the treatment in the absence of an antigen is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ, wherein introducing said target antigen and administering the treatment are performed independently in any order, and wherein said target antigen or epitope(s) thereof is introduced into the mammal by ingestion."

As noted above with regard to the rejection of Claim 55 over Dearman in view of Paul and Mitragotri, none of the references teach internal administration of an inducer of Langerhans cell migration. Accordingly, because not all of the elements of the claimed inventions are disclosed in the combination of references, the Examiner has failed to state a *prima facie* case of obviousness.

As has been discussed above, Dearman teaches that the function of topical DBP is to enhance the acquisition of FITC by Langerhans cells and suggest that the mechanism may be "altered penetration of the allergen through the skin". As taught by Mitragotri and others (Naik et al. 2000. Pharm. Sci. and Technol. Today 3:318-326), passive skin permeability to hydrophilic molecules >500 Da is essentially zero due to the barrier function of the stratum corneum. However, once a hydrophilic molecule >500 Da is past the stratum corneum, there is no barrier to diffusion (Naik et al. 2000. Pharm. Sci. and Technol. Today 3:318-326). Thus, a person with ordinary skill in the art at the time the invention was made would have concluded based on Dearman that delivery of an antigen to the gastrointestinal tract by ingestion would obviate the need for any other treatment (e.g., DBP to enhance permeation through the stratum corneum), because the gastrointestinal mucosa lacks a stratum corneum and the antigen would have direct access to immature dendritic cells resident in the specialized mucosal-associated lymphoid tissues. Dearman in view of Salyers therefore teaches away from the use DBP in situations wherein the antigen is introduced into a mammal by ingestion.

Contrary to the teachings of Dearman, the inventor discovered that exposing immature dendritic cells to a protein or peptide antigen does not induce the maturation and migration of antigen-bearing dendritic cells to draining lymphoid organs (see Figures 11 and 12 of the specification). Only the present invention teaches that there are lipophilic molecules ≤500 daltons that in the absence of antigen are able to induce immature dendritic cells to mature and migrate to draining lymphoid organs, thus providing the motivation to use such molecules in conjunction with delivery of an antigen to immature dendritic cells by ingestion.

Dearman fails to suggest to the skilled artisan that lipophilic molecules ≤500 daltons are able to induce immature dendritic cells to mature and migrate to draining lymphoid organs in the absence of an antigen (as recited in amended Claim 19). Salyers does not cure this failure. Therefore, a person with ordinary skill in the art at the time the invention was made would not have been motivated to combine ingestion of antigen with a topical treatment which in the absence of an antigen is capable of inducing immature dendritic cells to mature and migrate to the draining lymphoid organ, as recited in amended Claim 19. Therefore, Applicant respectfully suggests that Claim 19 is not obvious over Dearman in view of Salyers, and withdrawal of the rejection under §103 is therefore requested.

The Examiner rejected Claims 1, 6, 8, 11, 13-16, 27-31, 52, 53, 55, 56 and 58 under 35 U.S.C. §103(a) as being allegedly unpatentable over Dearman et al. in view of Glenn (US 5,980,898).

Claims 1, 6, 11, 13-16, and 27-31 recited a method for vaccinating a mammal against an antigen comprising *inter alia* introducing the antigen into the mammal by disrupting the stratum corneum. As detailed above, Dearman teaches that Langerhans cell acquisition of a contact hypersensitivity antigen can be facilitated by DBP by increasing permeation of such antigens through intact skin. Glenn teaches a method for vaccinating a mammal comprising the topical administration of an antigen in combination with an activator of Langerhans cells, wherein the activator is selected from the lipophilic molecules, trinitrochlorobenzene, dinitrofluorobenzene, pentadecylcatechol and lipid A. Because neither Dearman nor Glenn teach or suggest a vaccination method in which antigen is introduced into a mammal by disrupting the stratum corneum, the combination fails to set forth a *prima facie* case of obviousness. Indeed, both Dearman and Glenn teach away from methods that include a step of disrupting the stratum

corneum—as they are drawn to topical methods of immunization. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the §103 rejection of Claims 1, 6, 11, 13-16, and 27-31 over Dearman in view of Glenn.

Claims 52 and 53 recite: "[a] method for enhancing an immune response in a mammal against an endogenous antigen, comprising repeatedly topically administering to the mammal a lipophilic compound having a molecular weight ≤500 daltons, wherein the lipophilic compound is applied in an amount sufficient to increase the number of antigen-bearing dendritic cells presenting said endogenous antigen in a lymphoid organ, wherein said lipophilic compound is selected from the following formulas...".

Applicant respectfully points out that Lipid A is irrelevant to the present invention because it has a molecular weight of about 1,900 Da. Trinitrochlorobenzene, dinitrofluorobenzene, and pentadecylcatechol, disclosed by Glenn have molecular weights ≤500 daltons, but are contact hypersensitivity antigens. Claims 52 and 53 as currently amended recite the step of repeatedly topically administering the lipophilic compound without any added antigen. Dearman teaches that it is the antigen that induces maturation and migration of skin dendritic cells, and that DBP has no effect alone on maturation and migration of dendritic cells. Thus, one skilled in the art would not be motivated to repeatedly topically administer DBP alone (without any antigen introduction). Glenn teaches topical administration of lipophilic molecules that are contact hypersensitivity antigens—and thus, consistent with the teaching of Dearman would be expected to induce maturation and migration of dendritic cells. There is no teaching or suggestion in either reference to repeatedly administering a lipophilic compound that is not either itself an antigen or that is not administered together with an antigen. Moreover, because neither reference does repeatedly topically administer a lipophilic compound such as DBP (without an antigen), there can be no expectation of successful immunization against an endogenous antigen derived from the references. Accordingly, Applicant respectfully requests withdrawal of the §103 rejection of Claims 52 and 53.

Both independent Claims 55 and 58 recite methods for vaccinating a mammal against an antigen, comprising: ***injecting the mammal*** with an effective dose of the antigen. None of the cited references teach methods of introducing the target antigen via injection. Instead, Dearman and Glenn uniformly teach methods of introducing the antigens via permeation through intact skin. Thus, these references teach away from the claimed methods. It is also noted that Claim 55

has the further limitation of "...***administering internally to the mammal a treatment...***". Neither Dearman nor Glenn teach internal administration of an inducer of Langerhans cell migration—both references teach topical administration. Accordingly, because not all of the elements of the claimed inventions are disclosed in the combination of references, the Examiner has failed to state a *prima facie* case of obviousness. Claim 56 has been canceled.

In view of the foregoing, Applicant respectfully requests withdrawal of the §103 rejections of Claims 55 and 58 over Dearman in view of Glenn.

The Examiner rejected Claims 1, 6, 8, 11, 13-19, 21-24, 27-31, 51-53, 55, 56 and 58 under the judicially created doctrine of obviousness-type double patenting over claims 1-21 of US patent 6,210,672.

Applicant appreciates the Examiner's acknowledgement that a terminal disclaimer will be filed at the time allowable subject matter is indicated.

CONCLUSION

The Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefore, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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